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Vascular-Targeted Photodynamic Therapy (VTP)

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1. Introduction

Despite recent advances in surgery, chemotherapy, and radiation treatment, survival of patients with advanced malignancy remains suboptimal. Photodynamic therapy (PDT) is now established as a clinical treatment modality for various diseases including cancer (Dougherty et al., 1998). PDT involves the combined action of a photosensitizer, visible light of an appropriate wavelength and molecular oxygen to produce reactive oxygen species (ROS) like singlet oxygen, a short-lived species with highly cytotoxic effect (Dougherty et al., 1998, Solban et al., 2005). In biological system, the generated ROS trigger a cascade of biochemical effects that result in cell death. Singlet oxygen is thought to be the main mediator of cellular death, involving apoptotic and necrotic responses within treated tumours and produces microvascular injury leading to inflammation and hypoxia. PDT effects are mediated not only through direct killing of tumour cells but also through indirect effects, which involve both the initiation of an immune response against tumour cells and the destruction of tumour neovasculature. Indeed, the vascular effect plays a critical role in the eradication of tumour by PDT as it may cause deprivation of life-sustaining nutrients and oxygen supply from the existing blood vessels of the surrounding tissue. This present chapter will focus on recent and significant advances and developments in targeting strategies in PDT with the emphasis on vascular target specificity.

2. Targeted photodynamic therapy

In cancer treatment, PDT is a locoregional treatment used to reduce the volume of a tumour mass and obtain a radical cure of a small superficial tumour. PDT has been developed for the treatment of various cancers, e.g. esophagus (Radu et al., 2000), bronchi (Metz & Friedberg 2001, Savary et al., 1997), and bladder (Guillemain et al., 2001, Jichlinski &

Leisinger 2001), as well as for other non-oncological applications, such as for the treatment of age-related macular degeneration (AMD) (Brown et al., 2004). Moreover, PDT has also been used as a successful non-invasive therapeutic modality for treating cutaneous neoplasm (Fritsch et al., 1998, Karrer et al., 2001).

PDT can enhance the quality of life and lengthen survival. It has minimal side effects, selective and curative targeting therapy, no drug resistance and reduced toxicity that allows for repeated treatment (Dolmans et al., 2003). Thus, the successful of PDT will widely depend on the nature of the photosensitizer, which upon absorption of light, induces a chemical or physical alteration of another chemical entity. Early studies of photosensitizers for PDT were focused on a complex mixture of porphyrins named haematoporphyrin derivative (HpD), the first generation of photosensitizer.

One of the most clinically used photosensitizer is porfimer sodium (Photofrin®), a purified product from the HpD derivative. Photofrin® is the first drug approved by the Food and Drug Administration (FDA) (Konan et al., 2002). It has also been indicated for the treatment of superficial bladder cancer in Canada and early lung and advanced esophageal cancers in Netherlands and Japan. It has been used in thousands of patients for more than 20 years and no long-term safety issues have emerged. Despite its continuing effectiveness, Photofrin® has several disadvantages. The main disadvantages are the drug induces protracted skin photosensitivity and the initial selectivity for the tumour tissue remains low (Gilson et al., 1988, Moriwaki et al., 2001). These limitations led to the development of the second generation of photosensitizers.

One of the well known second generation photosensitizer is temoporfin (*meta*-tetra(hydroxyphenyl)chlorin, also known as *m*-THPC or Foscan®). It has been effectively used for the palliative treatment of head and neck cancers and it has received an approval in Europe for this indication in 2001. Nonetheless, like Photofrin®, temoporfin is also correlated with a pronounced skin photosensitivity, slow elimination from the blood compartment and weak selectivity between tumour and healthy tissue (Sharman et al., 1999). The disadvantages of temoporfin are contrast to Pd-bacteriopheophorbide (Tookad® or WST09) and its derivative WST11 which are believed to be purely vascular mediated (Woodhams et al., 2006). Moreover, Tookad® exhibits rapid elimination from the circulation and its plasma half-life is less than a few hours. Another second generation photosensitizer is benzoporphyrin derivative, verteporfin (Visudyne®), which was also recently approved, but it was only developed for the treatment of age-related macular degeneration, and not indicated for cancer treatment (Kertes 2006). Protoporphyrin IX (PpIX) is the one example of photosensitizers used for topical application to treat skin lesions. It can be produced in nucleated cells after topical application of either aminolevulinic acid (ALA) or methyl aminolevulinate (mALA) to the site of skin cancer or precancerous lesion (Vihinen et al., 2005). This discovery has resulted in the approval of ALA in the USA and mALA in Europe (Brown et al., 2004).

Thousands of patients have already been treated with PDT using the first and second generation of photosensitizers for a variety of advanced neoplasms, and have shown a great improvement in their quality of life and lengthened their survival. In spite of PDT advantages, it has a limitation in the cancer treatment due to the low of selectivity of photosensitizers; the ideal drug delivery system in PDT should be selectively accumulated in the tumour tissues and the delivery of therapeutic concentrations of photosensitizer to the target site with little or no uptake by non-target cells. However, the majority of photosensitizers are taken up non-selectively by all cell types, hence, they are found accumulated not only in tumour cells but also in normal cells.

This situation led to the development of the third generation of photosensitizers, a derivative of the second generation of photosensitizer attached to or introduced into chemical devices. The chemical devices inquiring some biological specificity to deliver or to target such drug for selective accumulation of photosensitizer or vectors with photosensitizer such as nanoparticles, liposomes and miscellaneous (Bechet et al., 2008). Indeed, the new generation of photosensitizers are being designed and developed to enhance selectivity and efficacy of PDT. This could be done by improving the existing photosensitizers, adding specific moieties and using delivery vehicles to specifically target these compounds (Sharman et al., 2004). Thus, targeted-PDT employing the improved photosensitizers could offer better advantage in delivering the photosensitizers across the cellular plasma membrane and resulting in intracellular accumulation of the photosensitizer. For example the use of nanoparticles or peptides as carriers of photosensitizers offer very promising approach for an ideal PDT targeting agent (Bechet et al., 2008). The advantages of targeting strategy include the selective targeted delivery of the photosensitizer to the tumour site that induces low toxicity and minimal damage to the normal tissues. This strategy contributes in the mechanism of PDT in cancer treatment through direct killing of tumour cells but also through indirect effects, which involves both the initiation of an immune response against tumour cells and the destruction of the neovasculature.

3. PDT - Tumour vascular targeting

The targeting of tumour vasculature has become a very promising area of focus for the development of new cancer therapeutics (Tozer et al., 2005). It is well known that solid tumours cannot grow larger than 1 mm³ without developing a vascular network (Siemann et al., 2004). This is due to the fact that when a tumour grows, its need for nutrients and oxygen increases, as well as the removal of metabolic waste, and consequently the number and size of blood vessels increase proportionately. In addition, to sustain the tumour growth, tumour tissues need to depend upon existing blood vessels as well as development of new blood vessels from the pre-existing vasculature (angiogenesis) for maintaining the blood supply. Tumour vasculature is also responsible for the progression of cancer from small, localized neoplasm to larger, growing and potentially spread cancer to other parts of the body.

The vessels that nourish tumours possess structural and functional properties different from those of normal vessels (Fig. 1). Normal vasculature is characterized by dichotomous branching, but tumour vasculature is unorganized and exhibits significant abnormalities in vessel architectures (tortuosity, dilatation, irregular branching, and lack of pericyte and basement membrane coverage) and functions (stagnant blood flow and increased vascular permeability) (Fukumura & Jain 2007). Moreover, tumour vasculature can present trifurcations and branches with uneven diameters. Perivascular cells in tumour vessels have abnormal morphology and heterogeneous association with vessels (McDonald & Choyke 2003).

The process of angiogenesis involves the initiation, progression and metastasis of smooth muscle and endothelial cells to invade, proliferate, migrate and survive in response to angiogenic stimuli, leading to the formation of new microvessels. This process is facilitated by a variety of proangiogenic factors that basically consist of four groups of proteins, which are the angiogenic factors, the integrins, the matrix metalloproteinases (MMP) and the

plasminogen activator system. The first class of angiogenic factors group is composed of molecules that promote endothelial cells survival and proliferation, including VEGFs, angiopoietins, epithelial growth factor (EGF), fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), placenta growth factor (PlGF), insulin-like growth factor (IGF), angiogenic cytokines such as interleukin-8 (IL-8) and their endothelial receptors. Among them, VEGF plays a critical role in vascular formation and it is the most potent angiogenic cytokines. It has been first characterized for its ability to induce vascular leakage and permeability and to promote vascular endothelial cell proliferation (Dvorak et al., 1999, Ferrara & Davis-Smyth 1997). Another group of proangiogenic factors is the molecules that related with the cell-cell and cell-matrix interactions, which provide signals for endothelial survival, adhesion and vascular integrity. This group consists of integrins and other adherent molecules. A selective expression of adhesion receptor, $\alpha_v\beta_3$ integrin, has been detected during tumour angiogenesis (Brooks et al., 1994a, Brooks et al., 1994b). The survival of new endothelial cells is increased by a specific signal following the recognition of $\alpha_v\beta_3$ integrin from its receptor. The other group of proangiogenic factors is matrix metalloproteinases which comprise a group of proteolytic enzymes that facilitate the propagation of tumour and break down the extracellular matrix (ECM), thereby facilitating cell motility and thus allow the migration of endothelial cells to form new vessels (Ahmad et al., 2010). The last group is a cascade of proteases called the plasminogen activator system which plays an important role during the process of angiogenesis.

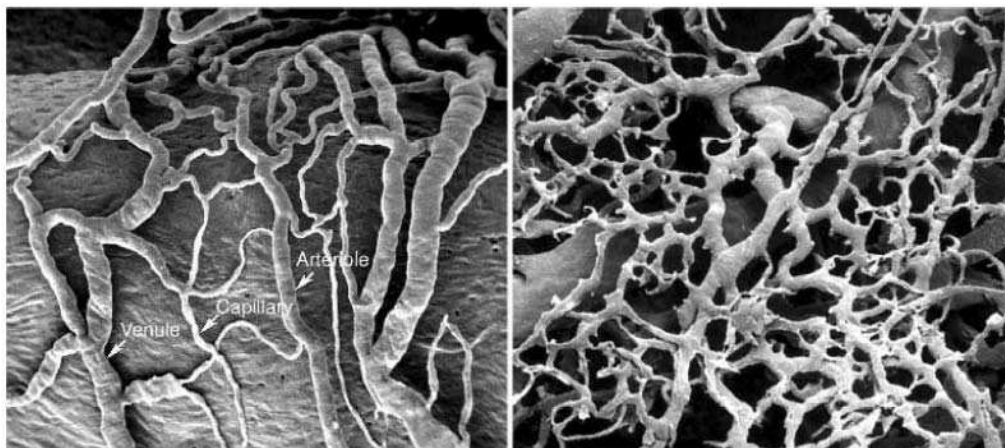


Fig. 1. Structural differentiation of normal blood vessels (*vasa vasorum* of carotid sinus rat, left) and tumour vasculature (human tumour xenograft in nude mice, right) using SEM microscopy (Konerding et al., 2001, McDonald & Choyke 2003).

On the basis of angiogenesis and vasculogenesis studies, Judah Folkman had proposed a hypothesis that "solid tumours are angiogenesis-dependent" and "anti-angiogenesis could be a potential therapeutic approach" (Folkman 1971). In his pioneer work, he found cancer cells implanted in vascular sites of animal grew rapidly and formed large tumours. In contrast, cells implanted in avascular sites were unable to form tumour masses more than 1 to 2 mm in size. Therefore, he proposed to inhibit the new blood vessels formation to prevent the tumour growth and thus kill cancer cells. Since then, it becomes a relevant target for tumour therapy. It gives some hopes that tumour growth can be interrupted or stopped by inhibiting the progression of angiogenesis and therefore destroys the tumour metastasis. In addition, the malignant tissue would be starved of its oxygen and nutrients supply and

also unable to eliminate metabolic wastes (Denekamp 1999). This also implies the destroying of tumour neovasculature, which can be an effective approach to control the tumour growth and provide the basis for selective tumour vasculature targeting.

Tumour vascular targeting can be divided into two general categories, anti-angiogenic therapy, referring to interfere with new blood vessel development and vascular targeted therapy, associating with the damage of the established tumour vasculature (Bloemendal et al., 1999, Ellis et al., 2001, Siemann et al., 2005, Siemann et al., 2004, Thorpe 2004). The inhibitors of anti-angiogenic therapy seek to inhibit or interrupt the tumour-initiated angiogenesis process by disrupting essential aspects of angiogenesis, particularly signaling between the tumour and endothelial cells, and between the tumour and stromal cells. In addition, anti-angiogenic therapy can disrupt endothelial function in order to prevent new blood vessel formation. Nevertheless, anti-angiogenic therapy is the other subject that can be discussed in another topic interest and will therefore not be discussed further in the present chapter.

Vascular targeted photodynamic therapy (VTP) is related to the destruction of functional vasculature which is necessary for efficient tumour eradication by PDT. The strategy aims to destroy neovasculature of tumours. Thereby, vascular damage is considered to be a major phenomenon occurring during PDT of tumours, which largely contributes to its efficacy. Vascular targeting in PDT is considered active when the photosensitizing compounds selectively accumulate in the targeted neovascular components, thus bringing out a preferential vascular response (B. Chen et al., 2006a). Vascular targeting can be passive when the injected photosensitizer is mainly confined in the blood vessels and reaches peak plasma concentration and will further provide a therapeutic window for vascular treatment. Recently, a combination of vascular targeted strategy and photodynamic therapy named vascular targeted photodynamic therapy (VTP) has become a promising subject to be explored and developed. VTP is being developed either by changing PDT schedule, for example, decrease the period between the photosensitizer's injection and irradiation of the tumour site (drug-light interval, DLI) or by designing photosensitizers localizing primarily in the vascular compartment (Star et al., 1986, Fingar et al., 1996, Kurohane et al., 2001).

VTP has several advantages, which are:

- i. the tumour endothelial cells are directly accessible to intravenously administered photosensitizer thus permitting a rapid localization of a high percentage of the injected dose
- ii. the molecular oxygen required for photochemical reaction is also more readily available
- iii. since each capillary provides oxygen and nutrients and also removes the metabolic wastes for thousands of tumour cells, occlusion of the vessel has an amplified effect on tumour cells
- iv. the outgrowth of mutant endothelial cells lacking the target antigen is unlikely because they are a normal, genetically stable cells population
- v. finally, since tumour vessels share common morphological and biochemical properties, this strategy should be applicable to different tumour types (Veikkola et al., 2000).

For example, the use of hematoporphyrin in the tumour cell death after photoirradiation by PDT is caused by vasoconstriction and complete stasis that occurs secondary to demolish the microvasculature (Star et al., 1986). It changes the morphological of neovasculature which led to the absence of the capillary layer and mitochondrial degeneration, thus supporting tumour demolition (Chaudhuri et al., 1987). By using vertoporphin in VTP, it resulted to cause a dose- and time-dependent increase in vascular permeability, but

decrease in blood perfusion. Vertoporphin in VTP is known to permeabilize blood vessels through the formation of endothelial intercellular gaps, hence, triggering the loss of endothelial barrier function that enhance the tumour vascular shutdown (Chen et al., 2008, Chen et al., 2006b). Another example is Photofrin® which induces changes in vessel constriction, vessel leakage and thrombus formation (Fingar et al., 1992), while higher dosage of Photofrin® during PDT causes vessel constriction and changes in permeability (Fingar et al., 1997).

With these several advantages, tumour targeting has become a promising strategy for the development of active photosensitizer delivery systems that able to enhance selectivity and efficiency of vascular PDT for cancer treatment. The next subtopic will focus on the main molecular targets explored in the vascular-targeting PDT for cancer, including the vascular endothelial growth factor receptors (VEGFRs such as neuropilin-1 (NRP-1)), $\alpha_v\beta_3$ integrin, matrix metalloproteinase (MMPs) and receptor tissue factor (TF) activities.

3.1 Vascular Endothelial Growth Factor (VEGF) receptors

Vascular endothelial growth factor (VEGF) is an endothelial cell -specific mitogen for vascular endothelial cells which is an important regulator of normal and pathological angiogenesis including cells survival and proliferation (Ferrara 2002, Ferrara & Davis-Smyth 1997). VEGF is upregulated in the bulky neoplastic cells, generally as a response to hypoxia and many oncogenes, and its overproduction is correlated with high microvascular density and poor prognosis (Ishigami et al., 1998). VEGF encourages the growth of vascular endothelial cells derived from arteries, veins, and lymphatics. VEGF induces a strong angiogenic response in a variety of both *in vivo* (Leung et al., 1989, Plouet et al., 1989) and *in vitro* models (Pepper et al., 1994) and also inducing confluent microvascular endothelial cells to invade collagen gels and form capillary-like-structures (Pepper et al., 1992).

The overexpression of VEGF results in the upregulation of VEGF receptors namely VEGFR-1 (also known as fms-like tyrosine kinase, flt-1), VEGFR-2 (fetal liver kinase-1, flk-1 or kinase domain region, KDR) and VEGFR-3 (KDR/flt-1) (Bando et al., 2005, Kremer et al., 1997, Plate et al., 1992). VEGFR-1 and VEGFR-3 are expressed in distinct vascular beds, whereas VEGFR-2 is selectively expressed on almost all endothelial cells (Ferrara 2004). VEGFR-1 and VEGFR-2 are associated with angiogenesis, while VEGFR-3 is affiliated with lymphangiogenesis (Ferrara 2004).

Among of the three primary receptors of VEGF, VEGFR-2 becomes an interest for most active targeting strategies and this receptor is believed to be the main receptor that mediates VEGF biological activities and also plays a major role in tumour-associated angiogenesis. VEGF/VEGFR-2 signaling pathway is critical for tumour angiogenesis and for solid tumour growth. Expression of VEGFR-2 in various cell types results in the ability to respond ligands by the transduction of a mitogenic signal. VEGFR-2 is highly expressed in both vascular endothelial cells and lymphatic endothelial cells in tumour neovasculature, as well as other cell types such as megakaryocytes (Katoh et al., 1995), hematopoietic stem cells (Katoh et al., 1995), and chronic myelogenous leukemia (CML) (Grosskreutz et al., 1999, Ishida et al., 2001). Therefore, VEGFR-2 is seen as promising molecular target for anti-angiogenic drug delivery, and that specific targeting of VEGFR-2 could provide an interesting approach for selective and efficient photosensitizer delivery to tumour neovasculature.

Although VEGFR-2 has been widely known as a promising target for the selective delivery of therapeutic drugs for conventional therapies, the number of photoactivatable drugs

targeting VEGFR-2 remains limited. Targeted verteporfin (Visudyne®) has been reported as the first research works that investigated the potential of VEGFR-2 as a molecular target for vascular PDT. In a recent study Renno *et al.* conjugated the verteporfin, first to polyvinyl alcohol (PVA) polymer, then to a peptidic motif ATWLPPR which was reported to bind VEGFR-2. The use of the conjugated drug efficiently caused choroidal neovascularization (CNV) closure and exhibited more selective than nonconjugated verteporfin (Renno *et al.*, 2004). Although these results showed the targeting VEGFR-2 can be an effective strategy to the tumour neovasculature, more recent studies demonstrated a contrast finding that ATWLPPR does not recognize KDR but bind to NRP-1 (Perret *et al.*, 2004, Tirand *et al.*, 2006). These results have then attracted a great interest on the potential of NRP-1 as promising target for targeted vascular PDT.

The neuropilins were originally reported as a mediator of axon guidance and later serve as a receptor that involved in normal blood vessel development, tumour angiogenesis and tumour progression (Ellis 2006, Favier *et al.*, 2006, Gu *et al.*, 2002, Neufeld *et al.*, 2002). Therefore, neuropilins appear to serve as a co-receptor or a 'hub' receptor due to its ability to bind with high affinity into two structurally unrelated classes of ligands with distinct biological functions, the class 3 semaphorins and various members of the VEGF family. As co-receptors of VEGF, the neuropilins have been identified to modulate binding to other receptors without being active in signaling (Soker *et al.*, 1998) and thought to increase the binding affinity of the various VEGF ligands to the primary receptors. Neuropilins are described in two family members, neuropilin-1 (NRP-1) and neuropilin-2 (NRP-2). NRP-1 was identified at first as high-affinity cell surface receptors for secreted class 3 semaphorins, but more recently, it was reported as a co-receptor for VEGF. NRP-2 was recognized by sequence analysis and it was reported to share the same domain arrangement as NRP-1 and also share with 44% identity with NRP-1 (Chen *et al.*, 1997, Kolodkin *et al.*, 1997).

Neuropilins are expressed specifically in tumour angiogenic vessels and some tumour cells, and also promote tumour angiogenesis and progression (Miao *et al.*, 2000). When co-expressed with VEGFR-2, NRP-1 enhanced the binding of VEGF₁₆₅ to VEGFR-2. This situation can be explained when the NRP-1 serve as a receptor for the VEGF₁₆₅ isoform through the exon 7-encoded region of VEGF (Soker *et al.*, 1998). VEGF₁₆₅ has also been shown to bind with the receptors VEGFR-1 and VEGFR-2 via the exons 3-and 4-encoded peptides, respectively (Keyt *et al.*, 1996). This situation leads the VEGF₁₆₅ to form a bridge between VEGFR-2 and NRP-1 (Soker *et al.*, 1998), and thus mediate the formation of a ternary complex between VEGF₁₆₅, VEGFR-2 and NRP-1 (Fuh *et al.*, 2000, Soker *et al.*, 2002, Staton *et al.*, 2007). It may explain the possible reason why NRP-1 enhances VEGF binding and activity by bringing these receptors into closer proximity (Soker *et al.*, 2002, Soker *et al.*, 1998). Besides that, NRP-1 co-expression with VEGFR-2 enhanced VEGF-induced chemotaxis in comparison with cells expressing VEGFR-2 alone, and also enhanced the VEGF binding to VEGFR-2, VEGFR-2 phosphorylation and VEGF-induced signaling and migration (Bernatchez *et al.*, 2002, Rollin *et al.*, 2004). Therefore, NRP-1 has become a promising target for selective vascular localization of photosensitizers, and thus enhances the vascular photodynamic effects.

In conjunction with that, our group introduced the conjugation of a photosensitizer (5-(4-carboxyphenyl)-10,15,20-triphenyl-chlorin, TPC) to a VEGF receptor-specific heptapeptide, H-Ala-Thr-Trp-Leu-Pro-Pro-Arg-OH (ATWLPPR), via a spacer (6-aminohexanoic acid, Ahx), noticed TPC-Ahx-ATWLPPR (Fig. 2) (Tirand *et al.*, 2006). We showed that ATWLPPR

and TPC-Ahx-ATWLPPR bound exclusively to NRP-1 but were devoid of affinity for VEGFR-2 or KDR, to which ATWLPPR was originally thought to bind. This peptide conjugation ATWLPPR has proved to be very efficient in endothelial cells compared to its nonconjugated counterpart. Our study demonstrated that TPC-Ahx-ATWLPPR accumulated up to 25-fold more in human umbilical vein endothelial cells (HUVEC) than free TPC over a 24 hours period. The accumulation of the conjugated photosensitizer was related to NRP-1-dependent mechanisms but also to non-specific mechanisms (Thomas et al., 2008, Tirand et al., 2007). *In vivo* biodistribution studies in nude mice xenografted with U87 human malignant glioma cells revealed significant tumour level to normal ratios as early as 1 hour after intravenous injection of TPC-Ahx-ATWLPPR. We also studied the *in vivo* vascular effect by measuring the tumour blood flow during PDT using both conjugated and nonconjugated photosensitizer (Fig. 3). Only the conjugate-mediated VTP produced a selective vascular effect, leading to vascular shutdown and tumour growth delay (Bechet et al., 2010).

From the biological mechanism point of view, the conjugate-mediated vascular effect implies the induction of tissue factor (TF) expression leading to the thrombogenic effect within the vessel lumen (Fig. 4) (Bechet et al., 2010).

These findings shed some light that the targeting strategy using a peptide competing with VEGF₁₆₅ binding on NRP-1 could have a better accumulation of photosensitizer in endothelial cells lining tumour vessels. Nonetheless, using this strategy, the affinity of conjugated photosensitizer for NRP-1 remains low compared to the peptide alone. The possible reason may include, (i) intramolecular interactions between chlorin and peptide, and steric hindrance due to the TPC moiety, (Ishigami et al., 1998) (ii) aggregation of the photosensitizer molecules, and (iii) low stability of the peptide moiety that, may be due to sensitivity to circulating peptidases action. In order to overcome these drawbacks, a linker can be used as a spacer to couple the photoactivable compound to the peptides, in order to individualize these two moieties. The bioavailability of the peptide can also be enhanced by the introduction of a non-amidic moiety at the cleavage site (Pernot et al, 2011).

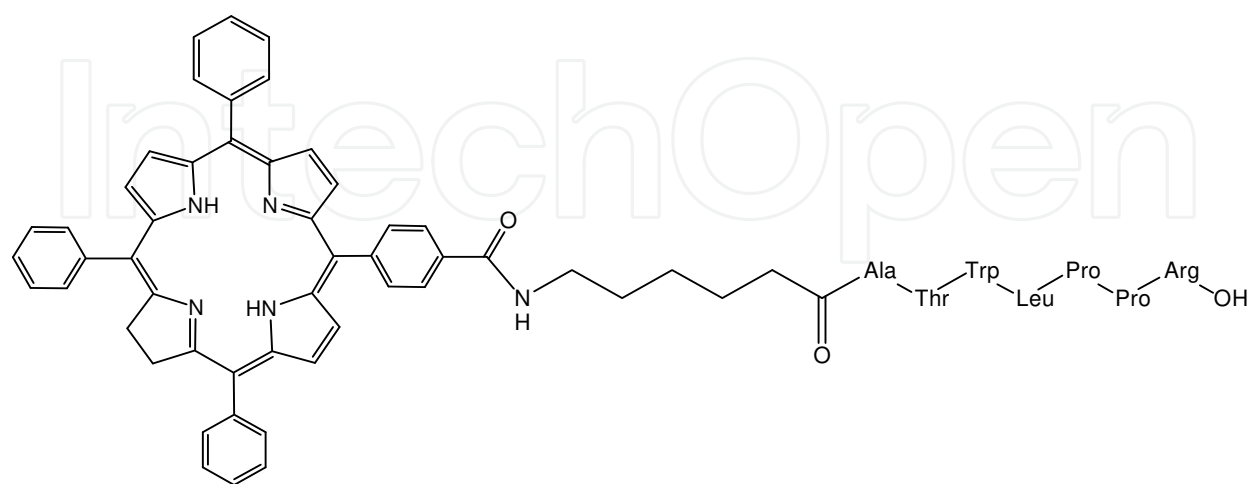


Fig. 2. ATWLPPR peptide conjugated with a chlorin (Tirand et al., 2006)

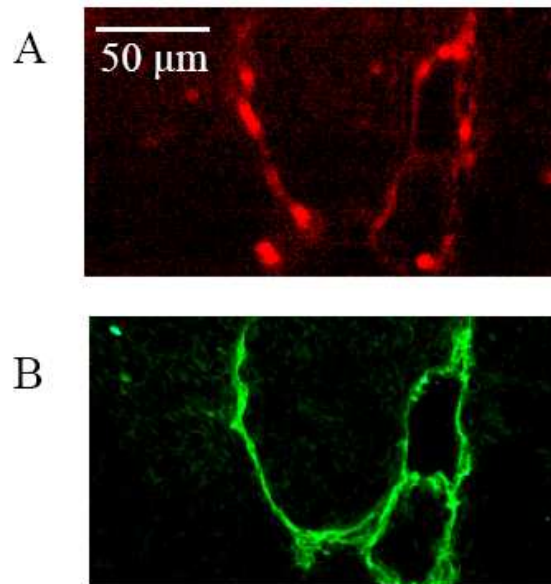


Fig. 3. Localization of the photosensitizers 4 hours after intravenous injection. (A) Color composite image of TPC-Ahx-ATWLPPR fluorescence (red). (B) Color composite image of CD31-staining (green) in the same region as (A). Analysis of the tumour sections 4 hours after TPC-Ahx-ATWLPPR administration showed that the photosensitizer was mainly colocalized inside the vascular endothelium (Thomas et al., 2008).

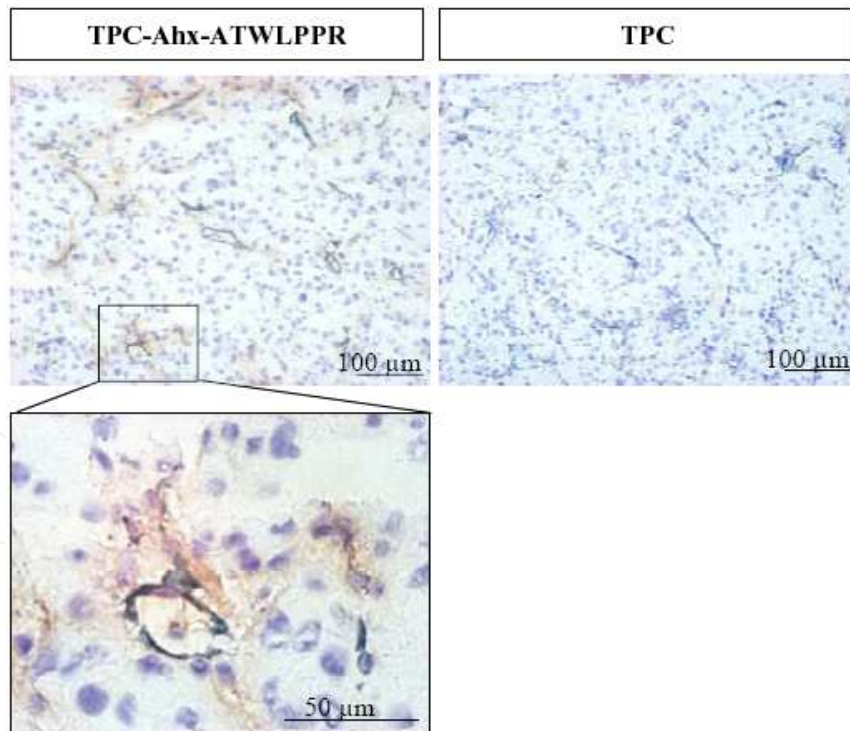


Fig. 4. Immediately after PDT, TPC-Ahx-ATWLPPR-induced (*upper left*) photodynamic activity induced TF expression (brown staining) compared to the nonconjugated photosensitizer (TPC) (*upper right*). Tissue factor staining appeared to be non-uniform and was not limited to vessel *lumen* areas but also present in tumour tissues. *Bottom* is the enlarged view of the corresponding specimen (Bechet et al., 2010).

3.2 $\alpha_v\beta_3$ Integrin

The $\alpha_v\beta_3$ integrin, a heterodimeric transmembrane glycoprotein receptor is highly expressed in many tumour cells including osteocarcinomas, neuroblastomas and lung carcinomas. The $\alpha_v\beta_3$ integrin is upregulated in both tumour cells and angiogenic endothelial cells (Desgrosellier & Cheresh 2010) but poorly expressed in resting endothelial cells and most normal organs. This integrin serves as an endothelial cell receptor for extracellular matrix proteins which includes fibrinogen (fibrin), vitronectin, thrombospondin, osteopontin and fibronectin (Desgrosellier & Cheresh 2010), and plays an important role in the calcium-dependent signaling pathway leading to endothelial cell migration (Byrne et al., 2008). Linear and cyclic derivatives of RGD peptidic motif (H-Arg-Gly-Asp-OH) are the well characterized oligopeptides known to bind to endothelial $\alpha_v\beta_3$ integrin. Therefore, $\alpha_v\beta_3$ integrin is believed as an attractive molecular target for antivascular therapies. In this sense, several studies have been done to explore the potential of $\alpha_v\beta_3$ integrin in vascular-targeted PDT.

Solid phase synthesis of four porphyrin derivatives bearing the $\alpha_v\beta_3$ integrin ligand RGD peptide was reported by Chaleix *et al.* (Chaleix et al., 2004). Three of these porphyrin derivatives exhibited photodynamic activity on K562 leukemia cells to a degree comparable to that of Photofrin®. The same authors later described the synthesis of a cyclic dithiopentapeptide CRGDC, containing the RGD sequence which has been found to adopt conformations showing an increased affinity for integrins (Fig. 5) (Chaleix et al., 2004, Haubner et al., 2001). The replacement of the disulfide bonds of the cyclic peptide by carbon-carbon bond increases its stability and plasmatc residence time (Haubner et al., 2001). Carboxy-glucosylporphyrins coupled to this cyclic peptide *via* a spacer arm showed the same efficiency for singlet oxygen production as hematoporphyrin under the same experimental conditions.

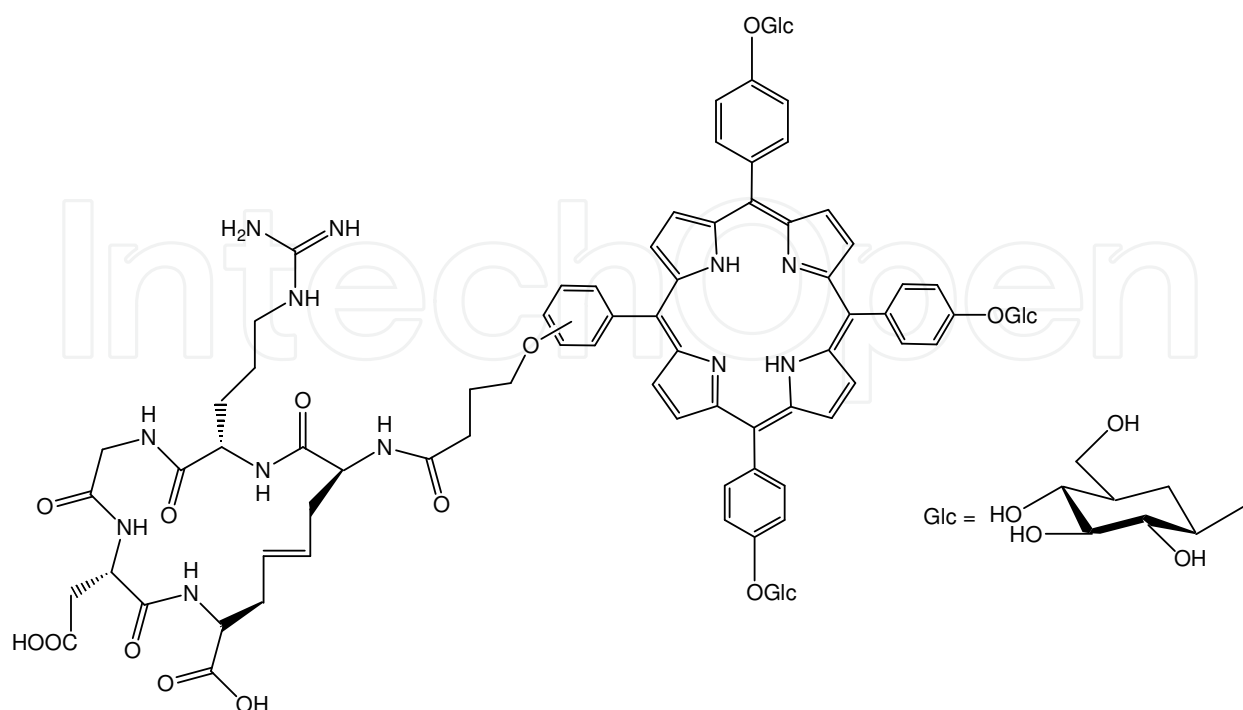


Fig. 5. Chemical structure of RGD-porphyrin conjugates prepared by Chaleix *et al.*, 2004.

In another study, Allen *et al.* tested the use of viral proteins as delivery vehicles for photosensitizer to enhance their target selectivity (Allen *et al.*, 1999). Adenoviruses most commonly caused illness of the respiratory system but they may also cause various other illnesses such as gastroenteritis, conjunctivitis, cystitis and rash illness. Adenoviruses received a great deal of attention as gene therapy vectors, due to ease and safe to manipulate and to store. Haddada *et al.* have shown that adenoviruses can infect several cell and tissue types including fully differentiated tissues and nonreplacing cells, and gain access into a cell *via* receptor-mediated endocytosis. This requires two separate receptors; one mediating attachment and the other mediating internalization. The first receptor allows the attachment of adenoviruses to cells *via* the fiber capsid protein/receptor interaction, while the second receptor, known as α_v integrin, is required for virus internalization. The binding of adenoviruses to α_v integrin is mediated by adenoviruses penton base proteins containing RGD peptide motif. Tetrasulfonated aluminum phthalocyanines (AlPcS₄) was covalently coupled to the various adenoviruses capsid proteins including the hexon, penton bases and fiber antigen *via* one or two caproic acid spacer chains, and these derivatives were tested both *in vitro* and *in vivo*. It was shown that the penton base conjugate was the most efficient *in vitro*, as measured in two positive cell lines (A549, Hep2) expressing integrins (Allen *et al.*, 1999). These findings suggested that adenoviral proteins can be used as delivery vehicles for photosensitizers to target tumour cells. However, vehicles may promote inflammation and anti-protein cellular immunity, which could limit their usefulness.

Some years ago, our group described a new family of peptidic photosensitizer by the conjugation of 5-(4-carboxyphenyl)-10,15,20-triphenylchlorin or porphyrin to the linear RGD or cyclic [RGDfK] motif (Frochot *et al.*, 2007). The results showed that RGD-containing linear or cyclic peptide targeted tetraphenylchlorin were incorporated up to 98- and 80-fold more, respectively, than the nonconjugated photosensitizer over a 24 hour exposure in HUVEC overexpressing $\alpha_v\beta_3$ integrin. However, we found a non-specific increased cellular uptake by murine mammary carcinoma cells (EMT-6), lacking $\alpha_v\beta_3$ integrin receptor. Survival measurements clearly demonstrated that HUVEC were more sensitive to peptide conjugate-mediated photodynamic therapy than the nonconjugated photosensitizer, demonstrating that the higher photodynamic efficiency was related to the high cellular uptake of the conjugate (Frochot *et al.*, 2007). Moreover, study showed that the peptide moiety also introduces a balance between hydrophilicity and hydrophobicity providing excellent water solubility and weak tendency to form aggregates, which is a required feature for an efficient photodynamic activity. More recently, our team has described the synthesis, characterization, fluorescence, and singlet oxygen quantum yields of tetraphenylporphyrin and tetraphenylchlorin coupled to RGD peptides and they found that some of these compounds are very promising for potential photodynamic therapy applications (Boisbrun *et al.*, 2008).

3.3 Matrix metalloproteinases

The matrix metalloproteinases (MMPs) are a family of extracellular proteinases (Fig. 6) that have an essential role in tumour metastasis and angiogenesis, more particularly in endothelial cell growth, invasion and migration, in the formation of capillary tubes and in the recruitment of accessory cells, due to its ability to degrade components of the extracellular matrix (ECM) (van Kempen *et al.*, 2006, Vihinen *et al.*, 2005). ECM is a complex network of macromolecules secreted by the cells, including carbohydrates and proteins such

as fibronectin, vitronectin, laminin, tenascin and collagen. While components of the ECM are involved in the regulation of different cell functions such as motility, morphogenesis, differentiation and proliferation, proteolytic degradation of the ECM is considered as an important mechanism favouring cancer development, invasion and metastasis, which is associated with increased expression of several proteases. Indeed, several studies have reported increased expression of proteases such as MMPs in many human malignant tissue types often correlating with poor prognosis (Egeblad & Werb 2002).

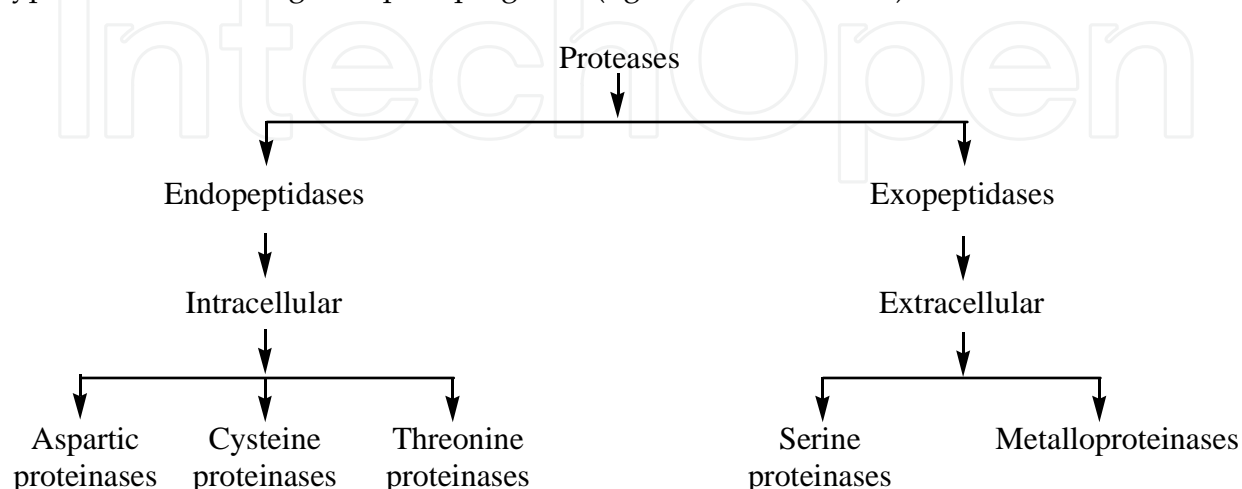


Fig. 6. Overview of different proteases.

MMPs-induced extracellular matrix proteolysis is also involved in the angiogenesis necessary for the continued growth of solid tumors. Indeed, MMPs are involved in different steps of angiogenesis (Chetty et al., 2010, Sharwani et al., 2006), thus become potential interesting targets in PDT for cancer treatment. MMPs facilitate endothelial cell migration by releasing them from their basement membranes, degrading perivascular ECM, and generating ECM degradation products that are chemotactic for endothelial cells. Fiore *et al.* demonstrated that MMPs have an ability to cleave not only components of the ECM, but also other proteinases, latent growth factors and growth factor binding proteins, chemotactic molecules, cell surface receptors and cell-cell adhesion molecules (Fiore et al., 2002). These findings came out with at least five main groups of MMPs; collagenases, gelatinases, stromelysins, the matrilysins and membrane-type MMPs, which differ according to their substrate specificity, primary structure and cellular localization.

MMPs are thought to play an important role at different stages of tumour development. Many studies offer strong evidence that MMP-2 (gelatinase A) and MMP-9 (gelatinase B) play a major role in the tumour growth and angiogenesis processes. These gelatinases can degrade the type IV collagen of basal laminae and other nonhelical collagen domains such as laminin (Chambers & Matrisian 1997, Xu et al., 2005). There is increasing evidence supporting the theory that MMP-2 and MMP-9 expression is associated with disease outcomes in different cancers such as ovarian and breast tumours (Davidson et al., 1999, Yoneda et al., 1997). Therefore, protease-sensitive macromolecular prodrugs have attracted interest for bio-responsive drug delivery to sites with up-regulated proteolytic activities.

Another interesting target is MMP-7, which is associated with many cancers. The MMPs regulate normal development but also play a role in the pathogenesis of cancers. MMP-7 in particular is found upregulated in several cancers including pancreatic, colon, breast, and non small-cell lung cancer (Leinonen et al., 2006, Shiomi & Okada 2003). Pham and co-

workers designed a peptide-based near-infrared (NIR) fluorescence probe consisting of a NIR fluorescence emitter linked *via* a MMP-7 substrate peptide linker to a NIR fluorescence absorber for sensing tumour-associated MMP-7 activity (Pham et al., 2004). They applied the Forster resonance energy transfer (FRET) principle for controlling fluorescence emission between the donor and the acceptor. The absence of proteases results in the quenched fluorescence for the donor; however, in the presence of proteases, the substrate peptide linker is cleaved, releasing the FRET interaction between the donor-acceptor fluorophore, which result in a four-fold increase in the fluorescence signal for an initially quenched molecular dye (Verma et al., 2007).

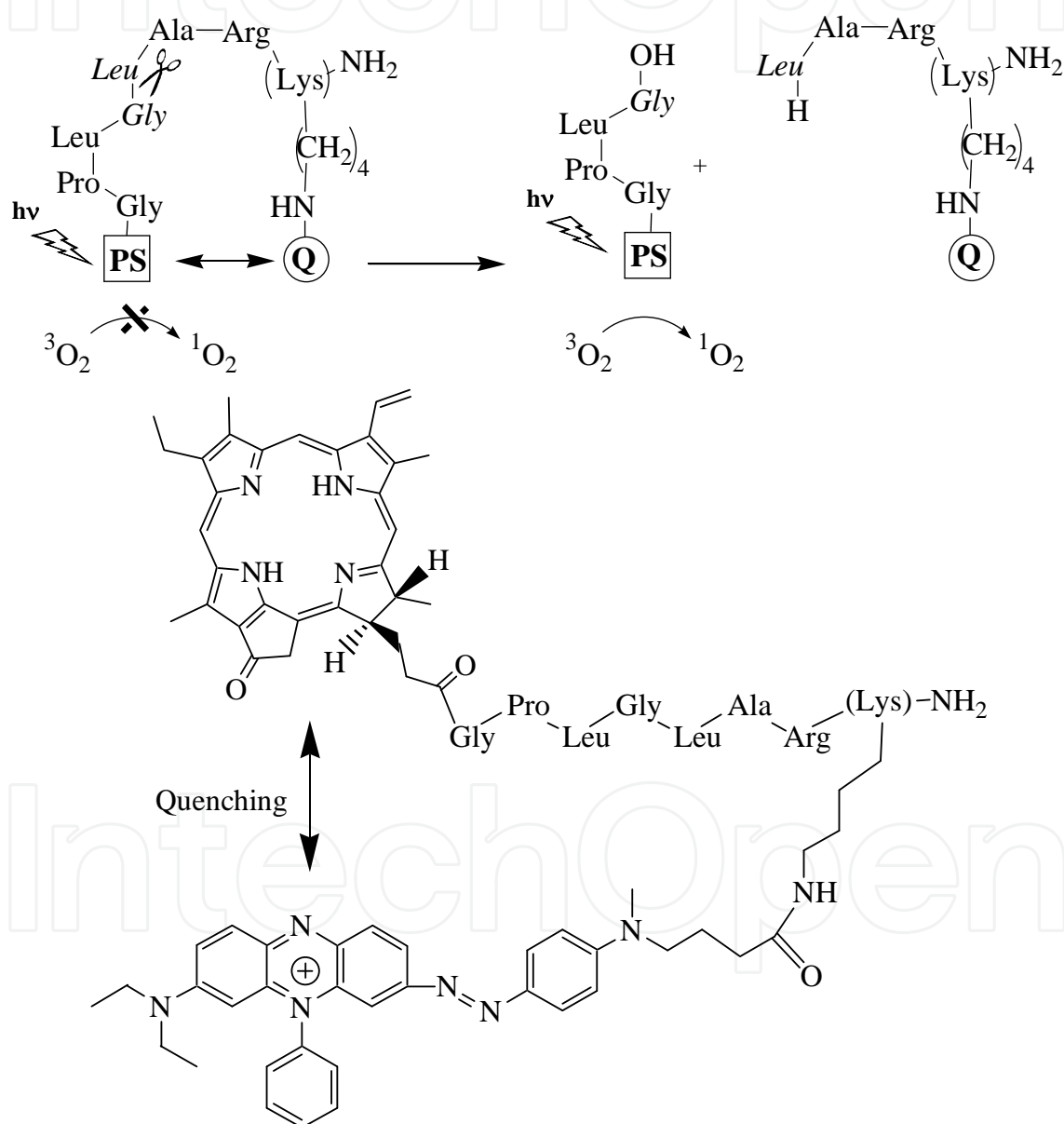


Fig. 7. MMP7-triggered photosensitizing molecular beacon concept. PS: photosensitizer, Q: quencher.

Considering this, photodynamic molecular beacons (PMB) provide an additional mechanism of selectivity in PDT over and above the targeting afforded by current

photosensitizers and specific light delivery (Zheng et al., 2007). Photodynamic molecular beacons consist of a disease-specific linker, a photosensitizer, and a fluorescence singlet oxygen quencher (Q). The photodynamic molecular beacons are noncytotoxic because of the energy transfer from the excited photosensitizer to quencher. Upon activation by the target enzyme, the linker will be cleaved, which allows the separation between the photosensitizer and the quencher. Upon irradiation, this leads to fluorescence emission restoration and singlet oxygen generation. Therefore, photodynamic molecular beacons offer a control of fluorescence emission and singlet oxygen generation of photosensitizer in response to specific cancer target activation. Thus, molecular beacons are FRET-based target-activatable probes.

Zheng *et al.* have combined the two principles of FRET and PDT and introduced a concept of photodynamic molecular beacons for controlling the photosensitizer's ability to generate singlet oxygen, and thus for controlling its PDT activity (Zheng et al., 2007). They reported the synthesis and characterization of a MMP-7-triggered photodynamic molecular beacon, using: (i) pyropheophorbide as the photosensitizer, because of its excellent singlet oxygen quantum yield, NIR fluorescence emission and high tumour affinity; (ii) black hole quencher 3 (BHQ3) as a dual fluorescence and singlet oxygen quencher; and (iii) a short peptide sequence, *GPLGLARK*, as the MMP-7 cleavable linker, with the cleavage site, as indicated by italics in Fig. 7 (Ishigami et al., 1998). This figure shows that the pyropheophorbide and the quencher are linked to the opposite ends of the MMP-7-specific cleavable peptide linker to keep them in close proximity, permitting FRET and singlet oxygen quenching to form inactive prodrug; silent and photodynamically inactive, until the linker interacts with the target tumour-associated MMP-7. After characterizing the MMP-7-triggered production of singlet oxygen in solution, the authors also demonstrated the MMP-7-mediated photodynamic cytotoxicity in cancer cells. *In vivo* studies revealed the MMP-7-activated PDT efficacy (Zheng et al., 2007). This finding validated the main principal of the photodynamic molecular beacons concept demonstrating that selective PDT-induced cell death can be achieved by controlling of the photosensitizer's ability to produce singlet oxygen.

3.4 Receptor Tissue Factor (TF)

Tissue factor (TF) is a transmembrane receptor protein that belongs to the class II cytokine receptor family. It is known to bind with high affinity to its endogenous ligand coagulation factor VII (fVII), thus initiating the blood coagulation cascade *via* the extrinsic pathway (Nemerson 1988). In addition to its role in coagulation, accumulating studies suggest that receptor TF regulates intracellular signaling pathway (Spek 2004), play an important role in embryonic development (Pedersen et al., 2005), inflammation (Chu 2005), angiogenesis (Chen et al., 2001) and, tumour growth and metastasis (Versteeg et al., 2004). Many studies revealed that receptor TF is expressed on endothelial cells of pathological blood vessels associated with solid tumours (Chen et al., 2001, Contrino et al., 1996, Hu & Garen 2000, 2001, Hu et al., 1999, Shoji et al., 1998, Tang et al., 2007), wet macular degeneration (wMD) (Bora et al., 2003, Tezel et al., 2007) and endometriosis (Krikun et al., 2010), but not on endothelial cells of normal blood vessels (Contrino et al., 1996, Drake et al., 1989, Hu & Garen 2000, 2001, Hu et al., 1999, Mulder et al., 1995, Osterud 1997, Rao & Pendurthi 1998, Tang et al., 2007). It has also been reported that VEGF protein secreted by tumour cells induces endothelial cells in tumour vasculature to express receptor TF (Clauss et al., 1990, Zucker et al., 1998). All these findings suggest that receptor TF provide accessible and specific therapeutic target for tumour cells and tumour vasculature (Shoji et al., 2008).

According to that, several strategies have been developed to target cancer cells and tumour neovasculature for alternative treatment using fVII as a drug carrier.

Hu *et al.* developed a ligand-targeted photodynamic therapy system by conjugating factor VII protein with verteporfin (Hu *et al.*, 1999). The fVII-targeted verteporfin PDT and non-targeted verteporfin have been tested both *in vitro* and *in vivo* to kill breast cancer cells and VEGF-stimulated vascular endothelial cells, and to inhibit the tumour growth of breast tumours in mouse xenograft model (Hu *et al.*, 2010). Their results showed that: (i) fVII protein could be conjugated to verteporfin without affecting its binding activity; fVII-targeted PDT could selectively kill receptor TF-expressing breast cancer cells and VEGF-stimulated angiogenic HUVECs but no side effect on non-receptor TF expressing unstimulated HUVEC, CHO-K1 and 293 cells; (iii) fVII targeting enhanced the effect of verteporfin PDT by three to four-fold; (iv) fVII-targeted PDT induced significantly stronger levels of apoptosis and necrosis than non-targeted PDT; and (v) fVII-targeted PDT had a significantly stronger effect on inhibiting breast tumour growth in mice than non-targeted PDT (Hu *et al.*, 2010). Since receptor TF is expressed in many types of cancer cells including leukemia cells, and selectively on angiogenic vascular endothelial cells, these findings suggest that fVII-targeted PDT could have broad therapeutic applications for cancer treatment.

4. Conclusion

Vasculature damage is an important mechanism involved in PDT mediated tumour eradication. Vascular targeted photodynamic therapy (VTP) is developed and designed to further strengthen the vascular photosensitization effect by site-targeted delivery of photosensitizing agents to the vascular target. In addition, selective delivery of therapeutic amounts of photosensitizers in diseased tissues is recognized as an absolute requirement for efficient and safe PDT for the treatment of cancers. It gives a big challenge to extend the application of PDT for the treatment of a broad ranges of tumour types, as such modality present many advantages over the conventional therapies. To achieve this goal, the development in targeted PDT continues to take advantage of the advances in the characterization of molecular mechanisms of tumour development. A large variety of specific molecular targets have been characterized and explored in tumour targeting. Many photosensitizing agents have been elaborated and evaluated through both *in vitro* and *in vivo* studies; nevertheless, only very few have reached clinical evaluation phases. Each photosensitizer has specific characteristics, but none includes all the properties of an ideal photosensitizer. Although third-generation photosensitizers have been widely described for selective targeting, very few have been evaluated for clinical applications as the *in vivo* selectivity was not sufficiently high.

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Advances in Cancer Therapy

Edited by Prof. Hala Gali-Muhtasib

ISBN 978-953-307-703-1

Hard cover, 568 pages

Publisher InTech

Published online 21, November, 2011

Published in print edition November, 2011

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How to reference

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Ezatul Ezleen Kamarulzaman, Hamanou Benachour, Muriel Barberi-Heyob, Céline Frochot, Habibah A Wahab, François Guillemin and Régis Vanderesse (2011). Vascular-Targeted Photodynamic Therapy (VTP), *Advances in Cancer Therapy*, Prof. Hala Gali-Muhtasib (Ed.), ISBN: 978-953-307-703-1, InTech, Available from: <http://www.intechopen.com/books/advances-in-cancer-therapy/vascular-targeted-photodynamic-therapy-vtp->

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